

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number
WO 01/29009 A1(51) International Patent Classification: C07D 239/42,
401/12, A61K 31/505, A61P 9/14

(21) International Application Number: PCT/GB00/04043

(22) International Filing Date: 19 October 2000 (19.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9924862.7 20 October 1999 (20.10.1999) GB(71) Applicant (for all designated States except US): CELL-
TECH CHIROSCIENCE LIMITED [GB/GB]; 216 Bath
Road, Slough, Berkshire SL1 4EN (GB).

(72) Inventors; and

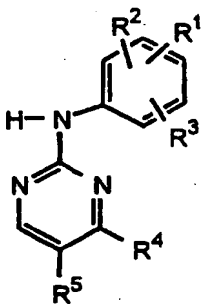
(75) Inventors/Applicants (for US only): DAVIS, Jeremy,
Martin [GB/GB]; 372 London Road, Wokingham, Berk-
shire RG40 1RE (GB). MOFFAT, David, Festus, Charles
[GB/GB]; 14 Lonsdale Way, Holyport, Maidenhead,
Berkshire SL6 2YX (GB).(74) Agents: HALLYBONE, Huw, George et al.; Carpmals
& Ransford, 43 Bloomsbury Square, London WC1A 2RA
(GB).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: 4,5-DISUBSTITUTED-2-AMINOPYRIMIDINES



(1)

(57) Abstract: Pyrimidines of formula (1) are described, wherein R¹ is a -XR⁶ group; R² and R³ which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, -OR¹⁰ [where R¹⁰ is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, -NO₂, -CN, -SR¹⁰, -COR¹⁰, S(O)R¹⁰, -SO₂R⁸, -SO₂N(R⁸)(R⁹), -CO₂R⁸, -CON(R⁸)(R⁹), -CSN(R⁸)(R⁹), -NH₂ or substituted amino group; R⁴ is a X¹R¹¹ group where X¹ is a covalent bond or a -C(R¹²)(R¹³)- [where each of R¹² and R¹³ is a hydrogen or halogen atom or a hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R¹¹ is an optionally substituted phenyl, thienyl, thiazolyl or indolyl group; R⁵ is a halogen atom or an alkynyl group; and the salts, solvates, hydrates and N-oxides thereof. The compounds are selective KDR kinase and/or FGFR kinase inhibitors and are of use in the prophylaxis and treatment of disease

states associated with angiogenesis.

WO 01/29009 A1

4.5-DISUBSTITUTED-2-AMINOPYRIMIDINES

This invention relates to certain 4,5-disubstituted-2-aminopyrimidines, to
5 processes for their preparation, to pharmaceutical compositions containing
them, and to their use in medicine.

Angiogenesis, the growth of capillaries from existing blood vessels, is an
essential process in normal embryonic development, tissue repair and
10 some aspects of female reproductive function. It is also associated with
the development of several pathological disorders including solid tumour
growth, metastasis, psoriasis and rheumatoid arthritis, as well as diabetic
retinopathy and age related macular degeneration (Folkman, Nature
Medicine, (1995) 1, 27-310).

15 Several growth factors have been shown to mediate angiogenesis through
alteration of vascular permeability, including vascular endothelial growth
factor (VEGF; G. Breier *et al.*, Trends in Cell Biology, 1996, 6, 454-6),
platelet derived growth factor (PDGF) and acidic and basic fibroblast
20 growth factors (a & b FGF).

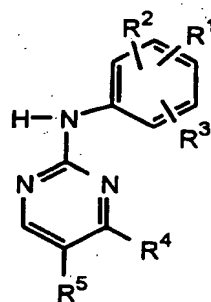
VEGF in dimeric form is a ligand that binds to two transmembrane tyrosine
kinase associated receptors, expressed exclusively on proliferating
endothelial cells, KDR (Flk-1 in mice) also known as VEGFR-2, and Flt-1
25 also known as VEGFR-1. Binding of VEGF to KDR/Flk and Flt leads to
receptor dimerisation, kinase activation, autophosphorylation of the
receptor and phosphorylation of intracellular substrates. An analogous
series of events ensues after ligand occupancy of the more widely
expressed tyrosine kinase associated FGFR receptor by aFGF or bFGF.
30 Thus receptor tyrosine kinase activity initiates a cellular signalling pathway
leading to proliferation.

Antagonism of VEGF with antibody completely suppresses
neovascularisation and growth of human rhabdomyosarcoma A673
35 spheroids in athymic mice (Borgstrom *et al*, Cancer Res., 1996, 56 4032-
4039). Suppression of bFGF gene expression by interferons α and β

inhibits capillary density in mice, leading to pancreatic eyelet tumour suppression (Folkman *et al*, Proc. Natl. Acad.Sci. 1996, 93, 2002 and Singh *et al* Proc.Natl. Acad. Sci. 1995, 92, 10457). Other receptor associated kinases such as PDGF β and EGFr may also have some role in mediating angiogenesis.

We have now found certain 4,5-disubstituted-2-aminopyrimidines which are potent and selective inhibitors of receptor tyrosine kinases involved in angiogenesis, especially KDR kinase and/or FGFr kinase. Selective inhibition of these kinases can be expected to have a beneficial effect and the compounds are thus of use in the prophylaxis and treatment of disease states associated with angiogenesis, as described hereinafter.

Thus, according to one aspect of the invention, we provide a compound of formula (1):



(1)

wherein R¹ is a -XR⁶ group [where X is a covalent bond, -O-, -S-, -C(O)-, -C(S)-, -C(O)O-, -S(O)-, -S(O)₂-, -CH₂-, -or N(R⁷)- [where R⁷ is a hydrogen atom or a straight or branched alkyl group] and R⁶ is a hydrogen or halogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, or a -NO₂, -CN, -SO₂N(R⁸)(R⁹) [where R⁸ and R⁹, which may be the same or different is a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], -CON(R⁸)(R⁹), -CSN(R⁸)(R⁹), -NH₂ or substituted amino group;

R² and R³ which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, -OR¹⁰ [where R¹⁰ is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, -NO₂, -CN, -SR¹⁰, -COR¹⁰, S(O)R¹⁰, -SO₂R⁸, -SO₂N(R⁸)(R⁹), -CO₂R⁸, -CON(R⁸)(R⁹), -CSN(R⁸)(R⁹), -NH₂ or substituted amino group;

R⁴ is a X¹R¹¹ group where X¹ is a covalent bond or a -C(R¹²)(R¹³)- [where each of R¹² and R¹³ is a hydrogen or halogen atom or a hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R¹¹ is an optionally substituted phenyl, thienyl, thiazolyl or indolyl group;

R⁵ is a halogen atom or an alkynyl group;

and the salts, solvates, hydrates and N-oxides thereof.

In the compounds of formula (1), the term "optionally substituted aliphatic group" when applied to each of the groups R², R³, R⁶ and R¹⁰ means each of these groups may independently be for example an optionally substituted C₁₋₁₀ aliphatic group, for example an optionally substituted straight or branched chain C₁₋₆ alkyl, e.g. C₁₋₃ alkyl, C₂₋₆ alkenyl, e.g. C₂₋₄ alkenyl, or C₂₋₆ alkynyl, e.g. C₂₋₄ alkynyl group. Each of said groups may be optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by X² [where X² is an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R¹⁴)- [where R¹⁴ is a hydrogen atom or a C₁₋₆ alkyl, e.g. methyl or ethyl, group], -CON(R¹⁴)-, -OC(O)N(R¹⁴)-, -CSN(R¹⁴)-, -N(R¹⁴)CO-, -N(R¹⁴)C(O)O-, -N(R¹⁴)CS-, -SON(R¹⁴), -SO₂N(R¹⁴), -N(R¹⁴)SO₂-, -N(R¹⁴)CON(R¹⁴)-, -N(R¹⁴)CSN(R¹⁴)-, -N(R¹⁴)SON(R¹⁴)- or -N(R¹⁴)SO₂N(R¹⁴) group] to form an optionally substituted R², R³, R⁶ and R¹⁰ heteroaliphatic group.

Particular examples of aliphatic groups represented by R², R³, R⁶ and/or R¹⁰ include optionally substituted -CH₃, -CH₂CH₃, -(CH₂)₂CH₃, -CH(CH₃)₂, -(CH₂)₃CH₃, -CH(CH₃)CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -(CH₂)₄CH₃, -(CH₂)₅CH₃, -CHCH₂, -CHCHCH₃, -CH₂CHCH₂, -CHCHCH₂CH₃, -CH₂CHCHCH₃, -(CH₂)₂CHCH₂, -CCH, -CCCH₃, -CH₂CCH, -CCCH₂CH₃, -CH₂CCCH₃, or -(CH₂)₂CCH groups. Where appropriate each of said groups may be optionally interrupted by one or

two atoms and/or groups X^2 to form an optionally substituted heteroaliphatic group. Particular examples include $-CH_2X^2CH_3$, $-CH_2X^2CH_2CH_3$, $-(CH_2)_2X^2CH_3$ and $-(CH_2)_2X^2CH_2CH_3$ groups.

- 5 The optional substituents which may be present on these aliphatic and/or heteroaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6} alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6} alkylthio e.g. methylthio or ethylthio, $-SC(NH)NH_2$, $-CH_2C(NH)NH_2$, amino, substituted amino, cyclic amino or heteroaromatic groups.

Substituted amino groups include for example groups of formulae $-NR^{15}R^{16}$ [where R^{15} is an optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl group optionally interrupted by one or two heteroatoms or
15 heteroatom-containing groups represented by X^3 (where X^3 is an atom or group as described above for X^2) and R^{16} is a hydrogen atom or is a group as just defined for R^{15}], $-N(R^{16})COR^{15}$, $-N(R^{16})CSR^{15}$, $-N(R^{16})SOR^{15}$, $-N(R^{16})SO_2R^{15}$, $-N(R^{16})CONH_2$, $-N(R^{16})CONR^{15}R^{16}$, $-N(R^{16})C(O)OR^{15}$, $-N(R^{16})C(NH)NH_2$, $-N(R^{16})C(NH)NR^{15}R^{16}$,
20 $-N(R^{16})CSNH_2$, $-N(R^{16})CSNR^{15}R^{16}$, $-N(R^{16})SONH_2$, $-N(R^{16})SONR^{15}R^{16}$, $-N(R^{16})SO_2NH_2$, $-N(R^{16})SO_2NR^{15}R^{16}$, or $-N(R^{16})Cyc^1$ [where Cyc^1 is an optionally substituted C_{3-7} monocyclic carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{14})-$, $-C(O)-$, $-C(S)-$, $-S(O)-$ or $-S(O_2)-$ groups].

- 25 Cyclic amino substituents which may be present on R^2 , R^3 , R^6 and/or R^{10} aliphatic or heteroaliphatic groups include groups of formula $-NHet^1$, where $-NHet^1$ is an optionally substituted C_{3-7} cyclic amino group optionally containing one or more other heteroatoms or heteroatom
30 containing groups selected from -O- or -S- atoms $-N(R^{14})-$, $-C(O)-$, $-C(S)-$, $-S(O)-$ or $-S(O_2)-$ groups.

Particular examples of amino, substituted amino and cyclic amino groups include $-NH_2$, methylamino, ethylamino, dimethylamino, diethylamino,
35 $-NHCyc^1$ where Cyc^1 is an optionally substituted cyclopentyl, cyclohexyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl,

piperazinyl or thiomorpholinyl group, or -NHet¹ where -NHet¹ is an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group. Optional substituents which may be present on these groups and substituted and cyclic amino groups in general include one, two or three halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁₋₄alkyl, e.g. methyl or ethyl, hydroxyl, C₁₋₄alkoxy, e.g. methoxy or ethoxy or pyridyl groups.

Optional heteroaromatic substituents which may be present on the aliphatic or heteroaliphatic groups represented by R², R³, R⁶ and/or R¹⁰ include those heteroaromatic groups described below in relation to R², R³, R⁶ and R¹⁰.

When R², R³, R⁶ and/or R¹⁰ is present in compounds of formula (1) as an optionally substituted cycloaliphatic group it may be an optionally substituted C₃₋₁₀ cycloaliphatic group. Particular examples include optionally substituted C₃₋₁₀cycloalkyl, e.g. C₃₋₇cycloalkyl, or C₃₋₁₀cycloalkenyl e.g. C₃₋₇cycloalkenyl groups.

Heteroaliphatic or heterocycloaliphatic groups represented by R², R³, R⁶ and/or R¹⁰ include the aliphatic or cycloaliphatic groups just described for these substituents but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups represented by X², where X² is as described above.

Particular examples of R², R³, R⁶ and/or R¹⁰ cycloaliphatic and heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5-cyclohexadien-1-yl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl,

isoxaziny, oxathiaziny, e.g. 1,2,5 or 1,2,6-oxathiaziny, or 1,3,5-oxadiaziny groups.

Optional substituents which may be present on R², R³, R⁶ and/or R¹⁰ cycloaliphatic and heterocycloaliphatic groups include those optional substituents described above for R⁶ when it is an aliphatic group. The heterocycloaliphatic groups may be attached to the remainder of the molecule of formula (1) through any appropriate ring carbon or heteroatom.

10

When R², R³, R⁶ and/or R¹⁰ is present as an aromatic group in compounds of formula (1) it may be for example an optionally substituted monocyclic or bicyclic fused ring C₆₋₁₂ aromatic group, such as an optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl group.

15

Heteroaromatic groups represented by R², R³, R⁶ and/or R¹⁰ include optionally substituted C₁₋₉ heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

20

25

Examples of heteroaromatic groups represented by R², R³, R⁶ and/or R¹⁰ include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethyl-imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl,

30

35

benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydro-
 5 isoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on any of the just described aromatic or heteroaromatic groups include one, two, three or more
 10 substituents, each represented by the group R^{17} as more particularly defined below in relation to the phenyl substituent R^{11} .

Substituted amino groups represented by the groups R^1 , R^2 and/or R^3 in compounds of formula (1) include for example the groups $-NR^{15}R^{16}$,
 15 $-N(R^{16})COR^{15}$, $-N(R^{16})CSR^{15}$, $-N(R^{16})SOR^{15}$, $-N(R^{16})SO_2R^{15}$, $-N(R^{16})CONH_2$, $-N(R^{16})CONR^{15}R^{16}$, $-N(R^{16})C(O)OR^{15}$, $-N(R^{16})C(NH)NH_2$, $-N(R^{16})C(NH)NR^{15}R^{16}$, $-N(R^{16})CSNH_2$, $-N(R^{16})CSNR^{15}R^{16}$, $-N(R^{16})SONH_2$, $-N(R^{16})SONR^{15}R^{16}$, $-N(R^{16})SO_2NH_2$, $-N(R^{16})SO_2NR^{15}R^{16}$, $-N(R^{16})Cyc^1$ where R^{15} , R^{16}
 20 and Cyc^1 are as defined above.

Halogen atoms represented by the group R^5 in compounds of the invention include fluorine, chlorine, bromine and iodine atoms. Alkynyl groups represented by R^5 include $-CCH$ and $CCCH_3$ groups.

25

The group R^{11} in compounds of formula (1) may be a phenyl or substituted phenyl group. The substituted phenyl group may contain one, two, three or more substituents, each represented by the group R^{17} .

30 The substituent R^{17} may be selected from an atom or group R^{18} or $-Alk(R^{18})_m$, where R^{18} is a halogen atom, or an amino ($-NH_2$), $-NHR^{19}$ [where R^{19} is an $-Alk(R^{18})_m$, heterocycloaliphatic, $-Alk$ -heterocycloaliphatic, aryl or heteroaryl group], $-N(R^{19})_2$ [where each R^{19} group is the same or different], nitro, cyano, hydroxyl ($-OH$), $-OR^{19}$, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), $-SR^{19}$, $-COR^{19}$, $-CSR^{19}$, $-SO_3H$,
 35 $-SO_2R^{19}$, $-SO_2NH_2$, $-SO_2NHR^{19}$, $SO_2N[R^{19}]_2$, $-CONH_2$, $-CSNH_2$,

-CONHR¹⁹, -CSNHR¹⁹, -CON[R¹⁹]₂, -CSN[R¹⁹]₂, -N(R¹⁴)SO₂H [where R¹⁴ is as defined above], -N(R¹⁴)SO₂R¹⁹, -N[SO₂R¹⁹]₂, -N(R¹⁴)SO₂NH₂, -N(R¹⁴)SO₂NHR¹⁹, -N(R¹⁴)SO₂N[R¹⁹]₂, -N(R¹⁴)COR¹⁹, -N(R¹⁴)CONH₂, -N(R¹⁴)CONHR¹⁹, -N(R¹⁴)CON[R¹⁹]₂, -N(R¹⁴)CSR¹⁹, -N(R¹⁴)CSNH₂,
 5 -N(R¹⁴)CSNHR¹⁹, -N(R¹⁴)CSN[R¹⁹]₂, -N(R¹⁴)C(O)OR¹⁹, or an optionally substituted cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk is a straight or branched C₁₋₆ alkylene, C₂₋₆ alkenylene or C₂₋₆ alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or S(O)-, -S(O)₂- or -N(R¹⁴)- groups; and m is zero or an integer 1,
 10 2 or 3.

When in the group -Alk(R¹⁸)_m m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R¹⁸ may be present on any suitable carbon atom in -Alk. Where more than one R¹⁸ substituent is
 15 present these may be the same or different and may be present on the same or different atom in -Alk or in R¹⁷ as appropriate. Thus for example, R¹⁷ may represent a -CH(R¹⁸)₂ group, such as a -CH(OH)Ar group where Ar is an aryl or heteroaryl group as defined below. Clearly, when m is zero and no substituent R¹⁸ is present the alkylene, alkenylene or alkynylene
 20 chain represented by Alk becomes an alkyl, alkenyl or alkynyl group.

When R¹⁸ is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

25 Esterified carboxyl groups represented by the group R¹⁸ include groups of formula -CO₂Alk¹ wherein Alk¹ is a straight or branched, optionally substituted C₁₋₈ alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C₆₋₁₂arylC₁₋₈alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthyl-
 30 methyl or 2-naphthylmethyl group; a C₆₋₁₂aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₂aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a pivaloyloxymethyl,
 35 propionyloxyethyl or propionyloxypropyl group; or a C₆₋₁₂aroyloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxyethyl or benzoyl-

oxypropyl group. Optional substituents present on the Alk¹ group include R¹⁸ substituents described above.

When Alk is present in or as a substituent R¹⁷ it may be for example a
5 methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R¹⁴)- groups.

10

When R¹⁸ is present in compounds of formula (1) as an optionally substituted cycloaliphatic group it may be an optionally substituted C₃₋₁₀ cycloaliphatic group. Particular examples include optionally substituted C₃₋₁₀cycloalkyl, e.g. C₃₋₇cycloalkyl, or C₃₋₁₀cycloalkenyl e.g. C₃₋₇cycloalkenyl groups.

15

Heterocycloaliphatic groups represented by R¹⁹ and when present R¹⁹ include the cycloaliphatic groups just described for R¹⁸ but with each group additionally containing one, two, three or four heteroatoms or
20 heteroatom-containing groups selected from -O- or -S- atoms or -N(R¹⁴)-, -C(O)-, -C(S)-, -S(O)- or -S(O₂)- groups.

Particular examples of R¹⁸ cycloaliphatic and R¹⁸ or R¹⁹ heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl,
25 cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5-cyclohexadien-1-yl, tetrahydrofuranyl, pyrrolidine, e.g. 2- or 3-pyrrolidinyl, pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl,
30 piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

35 Optional substituents which may be present on R¹⁸ cycloaliphatic and R¹⁸ or R¹⁹ heterocycloaliphatic groups include one, two, three or more

substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C₁₋₆alkoxy, e.g. methoxy or ethoxy, thiol, C₁₋₆alkylthio, e.g. methylthio or ethylthio, hydroxy, C₁₋₆alkyl, e.g. hydroxymethyl, hydroxyethyl, -CN, -NO₂, -NHR¹⁴ or -N(R¹⁴)₂ groups.

5

Aryl and heteroaryl groups represented by the group R¹⁸ or Ar include for example optionally substituted monocyclic or bicyclic C₆₋₁₂ aromatic groups, e.g. phenyl groups, or C₁₋₉ heteroaromatic groups such as those described above in relation to the group R⁶. Optional substituents which
10 may be present on these groups include one, two or three R^{18a} atoms or groups described below.

Particularly useful atoms or groups represented by R¹⁸, -Alk(R¹⁸)_m or R^{18a} as appropriate include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C₁₋₆alkylthiol e.g. methylthiol or ethylthiol, C₁₋₆alkoxy, e.g. methoxy or ethoxy, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, 1,1,3-trioxo-benzo[d]-thiazolidino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk¹ [where Alk¹ is as defined above], C₁₋₆alkanoyl e.g. acetyl, thiol
20 (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, -SC(NH₂⁺)NH₂, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido
30 (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino (-NHSO₂H), C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, e.g. 2-, 3- or 4- substituted phenylsulphonylamino such as 2-nitrophenylsulphonylamino, amino-

35

- sulphonylamino ($-\text{NHSO}_2\text{NH}_2$), C_{1-6} alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6} dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, phenylaminosulphonylamino, aminocarbonylamino,
- 5 C_{1-6} alkylaminocarbonylamino e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6} dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, phenylaminocarbonylamino, C_{1-6} alkanoylamino, e.g. acetylamino, optionally substituted phenylcarbonylamino, C_{1-6} alkanoylamino C_{1-6} alkyl, e.g. acetylaminomethyl, C_{1-6}
- 10 alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino, optionally substituted hetero C_{3-6} cycloalkyl, e.g. piperidinyl, piperazinyl, 4-(C_{1-6} alkyl)piperazinyl, e.g. 4-methylpiperazinyl, homopiperazinyl, or morpholinyl, optionally substituted hetero C_{3-6} cycloalkyl C_{1-6} alkyl, e.g. piperidinyl C_{1-6} alkyl, piperazinyl C_{1-6} alkyl, 4-(C_{1-6}
- 15 alkyl)piperazinyl C_{1-6} alkyl, e.g. 4-methylpiperazinylmethyl, or morpholinyl C_{1-6} alkyl, optionally substituted hetero C_{3-6} alkyl C_{1-6} alkylamino, optionally substituted hetero C_{3-6} cycloalkylamino, tetrazolyl, optionally substituted imidazolyl C_{1-6} alkyl, optionally substituted phenylamino, optionally substituted benzylamino, optionally substituted benzyloxy, or optionally
- 20 substituted pyridylmethylamino group.

Where desired, two R^{18} or $-\text{Alk}(\text{R}^{18})_m$ or R^{18a} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{2-6} alkylenedioxy group such as ethylenedioxy.

25

It will be appreciated that where two or more R^{18} , $-\text{Alk}(\text{R}^{18})_m$ or R^{18a} substituents are present, these need not necessarily be the same atoms and/or groups.

- 30 Especially useful R^{18} , $-\text{Alk}(\text{R}^{18})_m$ or R^{18a} substituents include for example fluorine, chlorine, bromine or iodine atoms, or a methylamino, ethylamino, hydroxymethyl, hydroxyethyl, methylthiol, ethylthiol, methoxy, ethoxy, n-propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 4-hydroxybutoxy, 2-aminoethoxy, 3-aminopropoxy, 2-(methylamino)ethoxy, 2-(dimethylamino)ethoxy,
- 35 3-(dimethylamino)propoxy, cyclopentyloxy, cyclohexyl, cyclohexylamino, 2-hydroxycyclohexylamino, trifluoromethyl, trifluoromethoxy, methylamino,

ethylamino, amino $(-\text{NH})_2$, aminomethyl, aminoethyl, dimethylamino, diethylamino, ethyl(methyl)amino, propyl(methyl)amino, 2-hydroxyethylamino, 3-hydroxypropylamino, 4-hydroxybutylamino, 2-aminoethylamino, 3-aminopropylamino, 4-aminobutylamino, 2-(methylamino)ethylamino, 2-(ethylamino)ethylamino, 2-(i-propylamino)ethylamino, 3-(i-propylamino)propylamino, 2-(dimethylamino)ethylamino, 3-(dimethylamino)propylamino, 2-(diethylamino)ethylamino, 3-(diethylamino)propylamino, 2-(methylamino)ethyl(methyl)amino, 3-(methylamino)propyl(methyl)amino, 2-(dimethylamino)ethyl(methyl)amino, 2-(dimethylamino)ethyl(ethyl)amino, nitro, cyano, hydroxyl $(-\text{OH})$, formyl $[\text{HC}(\text{O})-]$, carboxyl $(-\text{CO}_2\text{H})$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{OCH}_2\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{CH}_2\text{phenyl}$, t-butoxycarbonylmethoxy, acetyl, phenacetyl, thio $(-\text{SH})$, thiomethyl, thioethyl, $-\text{SC}(\text{NH})\text{NH}_2$, sulphonyl $(-\text{SO}_2\text{H})$, methylsulphonyl, methylaminosulphonyl, ethylaminosulphonyl, dimethylaminosulphonyl, diethylaminosulphonyl, carboxamido $(-\text{CONH}_2)$, methylaminocarbonyl, ethylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylaminocarbonylmethyl, $-\text{NHC}(\text{S})\text{NH}_2$, sulphonylamino $(-\text{NHSO}_2\text{H})$, methylsulphonylamino, ethylsulphonylamino, dimethylsulphonylamino, diethylsulphonylamino, sulphonylamino $(-\text{NHSO}_2\text{NH}_2)$, methylaminosulphonylamino, ethylaminosulphonylamino, dimethylaminosulphonylamino, diethylaminosulphonylamino, methylaminocarbonylamino, ethylaminocarbonylamino, dimethylaminocarbonylamino, diethylaminocarbonylamino, acetylamino, phenylcarbonylamino, aminomethylcarbonylamino, acetylaminomethyl, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, pyrrolidiny, piperidiny, piperaziny, 4-methylpiperaziny, homopiperaziny, morpholiny, pyrrolidiny $\text{C}_{1-6}\text{alkyl}$, piperidiny $\text{C}_{1-6}\text{alkyl}$, piperaziny $\text{C}_{1-6}\text{alkyl}$, 4-($\text{C}_{1-6}\text{alkyl}$)piperaziny $\text{C}_{1-6}\text{alkyl}$, morpholiny $\text{C}_{1-6}\text{alkyl}$, 2-pyrrolidinyethylamino, 2-(1-methylpyrrolidiny)ethylamino, 1-ethylpyrrolidinylmethylamino, piperidinylamino, 1-benzylpiperidinylamino, imidazolylmethyl, imidazolethyl, 4-(methoxy)phenylamino, 4-(3-hydroxypropyl)phenylamino, benzylamino, benzyloxy or pyridylmethylamino group.

When X^1 is present in compounds of the invention as a $(\text{R}^{12})(\text{R}^{13})$ - group it may be for example a $-\text{CH}_2-$ or $-\text{C}(\text{R}^{12})(\text{R}^{13})$ - group in which R^{12} and/or R^{13} is each a halogen atom such as a fluorine or chlorine atom or a

hydroxy, C₁₋₆alkyl e.g. methyl, ethyl or i-propyl, or C₁₋₆haloalkyl, e.g. trihalomethyl such as a trifluoromethyl group. Particular examples of such -C(R¹²)(R¹³)- groups include -CHF-, -CH(CH₃)-, -C(OH)(CF₃)- and -CH(CF₃)- groups.

5

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and

10

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or

15

napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts

20

such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, piperazine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include

25

pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

It will be appreciated that depending on the nature of the substituents R¹, R², R³ and R⁴ the compounds of formula (1) may exist as tautomers

30

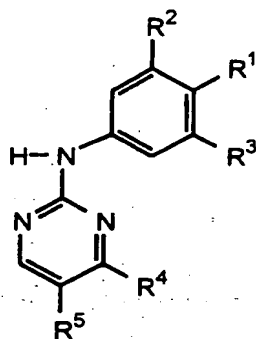
and/or geometrical isomers and/or may have one or more chiral centres so that enantiomers or diastereomers may exist. It is to be understood that the invention extends to all such tautomers and isomers of the compounds of formula (1), and to mixtures thereof, including racemates.

In the compounds according to the invention the group R⁴ is preferably a group X¹R¹¹ in which X¹ is a covalent bond.

35

The group R^5 in compounds of the invention is in particular a bromine or, especially a chlorine atom.

- 5 A particularly useful group of compounds according to the invention has the formula (1a):



(1a)

- 10 wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined for formula (1).

One particular class of compounds of formulae (1) and (1a) is that wherein one or both of R^2 and R^3 is a hydrogen atom. Compounds in which R^2 and R^3 is each a hydrogen atom are especially useful.

15

- In compounds of this class R^1 is in particular a group $-(Alk^2)_pNH_2$ (where Alk^2 is as defined above for Alk and p is zero or an integer 1), $-(Alk^2)_pNR^{15}R^{16}$ (where R^{15} and R^{16} are as defined above), $-(Alk^2)_pNHet^2$ (where $-NHet^2$ is as defined above for $NHet^1$), $-(Alk^2)_pOH$,
 20 and $-(Alk^2)_pAr$ (where Ar is a nitrogen-containing heteroaromatic group as defined above). Especially useful R^1 substituents include $-Alk^2NH_2$, particularly $-(CH_2)_2NH_2$ and $-C(CH_3)_2NH_2$, $-Alk^2NR^{15}R^{16}$, particularly $-CH_2N(CH_2CH_3)_2$ and $-(CH_2)_2NHC(CH_3)_3$, $-(Alk^2)_pNHet^2$ where $-NHet^2$ is an optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl group, $-Alk^2OH$, particularly $-(CH_2)_2OH$ and $-(Alk^2)_pAr$
 25 where Ar is an optionally substituted imidazolyl or benzimidazolyl group. Optional substituents which may be present on these particular $-NHet^2$ or

Ar groups include those generally and particularly described above in relation to the groups -NHet¹ and Ar.

5 In general in compounds of formulae (1) or (1a) R⁴ is preferably a group X¹R¹¹ in which X¹ is a covalent bond and R¹¹ is a phenyl or, especially, a substituted phenyl group containing one, two or three R¹⁷ substituents as defined herein. Particularly useful R¹⁷ substituents include -(Alk²)_pNH₂ substituents as just generally and particularly discussed for R¹.

- 10 Particularly useful compounds according to the invention include:
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[3-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;
15 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(1-imidazolyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
20 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
25 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-thiomorpholinoethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(tertbutylamino)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
30 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3,5-dimethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
35 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-(pyrid-2-yl)piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(pyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(piperidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;

- 5 (R)-4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3-dimethylaminopyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
and the salts, solvates, hydrates and N-oxides thereof.

10 Compounds according to the invention are potent and selective inhibitors of KDR and/or FGFr4 kinases as demonstrated by differential inhibition of these enzymes when compared to inhibition of other protein kinases such as EGFr kinase, p56^{lck} kinase, ZAP-70 kinase, protein kinase C, Csk kinase and p59^{fyn} kinase. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in
15 the Examples hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of diseases in which inappropriate KDR kinase action plays a role, for example in disease states associated with
20 angiogenesis. The compounds are then of use for example in the prophylaxis and treatment of cancer, psoriasis, rheumatoid arthritis, Kaposi's Sarcoma, ischemic heart disease, atherosclerosis and ocular diseases, such as diabetic retinopathy, involving retinal vessel proliferation and the invention is to be understood to extend to such uses and to the
25 use of a compound of formula (1) in the preparation of a medicament for the prophylaxis and treatment of such diseases.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and
30 according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form
35 suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection, including bolus injection or infusion or particle mediated injection. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials or a device containing a compressed gas such as helium for particle mediated administration. The compositions for bolus injection or infusion may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For

particle mediated administration the complex may be coated on particles such as microscopic gold particles.

5 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection. Where desired, the compounds according to the invention may also be conjugated to a polymer, e.g. a naturally occurring polymer such as albumin, to prolong the half life of the compounds when in use. Such
10 conjugates may be formulated and delivered as described above.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser,
15 with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

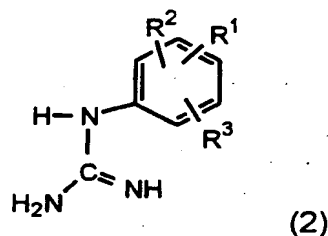
The compositions may, if desired, be presented in a pack or dispenser
20 device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or
25 treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for
30 parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

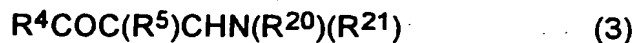
The compounds of the invention may be prepared by a number of
35 processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols

R¹, R², R³, R⁴ and R⁵ when used in the text or formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by reaction of a guanidine of formula (2):



or a salt thereof
with an enaminone of formula (3):

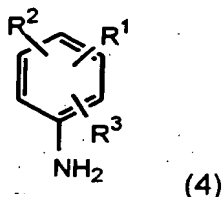


where R²⁰ and R²¹, which may be the same or different is each a C₁₋₆ Alkyl group.

The reaction may be performed in a solvent, for example a protic solvent such as an alcohol, e.g. ethanol, ethoxyethanol or propan-2-ol, optionally in the presence of a base e.g. an Alkali metal base, such as sodium hydroxide or potassium carbonate, at an elevated temperature, e.g. the reflux temperature.

Salts of the compounds of formula (2) include acid salts such as inorganic acid salts e.g. hydrochlorides or nitrates.

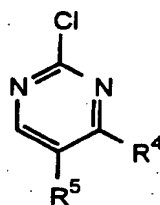
- 5 Intermediate guanidines of formula (2) may be prepared by reaction of the corresponding amine of formula (4):



- 10 with cyanamide at an elevated temperature. The reaction may be performed in a solvent such as ethanol at an elevated temperature, e.g. up to the reflux temperature. Where it is desired to obtain a salt of a guanidine of formula (2), the reaction may be performed in the presence of a concentrated acid, e.g. hydrochloric or nitric acid.
- 15 The amines of formula (4) are either known compounds or may be obtained by conventional procedures, for example by hydrogenation of the corresponding nitro derivatives using for example hydrogen in the presence of a metal catalyst in a suitable solvent, for example as more particularly described in the interconversion reactions discussed below.
- 20 The nitrobenzenes for this particular reaction are either known compounds or may be prepared using similar methods to those used for the preparation of the known compounds.

- 25 Intermediate enaminones of formula (3) are either known compounds or may be prepared by reaction of an acetyl derivative $R^4COCH_2R^5$ with an acetal $(R^{20})(R^{21})NCH(OR^{22})_2$ (where R^{22} is a C_{1-6} Alkyl group such as a methyl or ethyl group) at an elevated temperature. The starting materials for this reaction are either known compounds or may be prepared by methods analogous to those used for the preparation of the known
- 30 compounds.

In another process according to the invention, a compound of formula (1) may be prepared by displacement of a chlorine atom in a pyrimidine of formula (5):



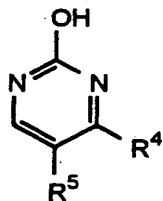
5

(5)

with an amine of formula (4)

The reaction may be performed at an elevated temperature, for example the reflux temperature, where necessary in the presence of a solvent, for example an alcohol, such as 2-ethoxyethanol or isopropanol, a cyclic ether, e.g. dioxane or a substituted amide such as dimethylformamide, optionally in the presence of a base, for example an organic amine such as pyridine.

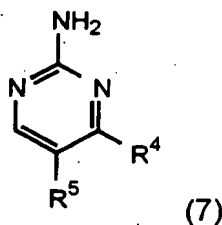
Intermediate pyrimidines of formula (5) may be obtained by reaction of a corresponding pyrimidine of formula (6):



(6)

with phosphorous oxychloride optionally in a solvent such as a substituted amide e.g. dimethylformamide at an elevated temperature, for example the reflux temperature.

Intermediates of formula (6) may be prepared from the corresponding amine of formula (7):



with sodium nitrite in an aqueous acid, e.g. aqueous sulphuric acid at around ambient temperature.

5

Amines of formula (7) may be prepared by reaction of an enaminone of formula (3) with a guanidine salt, e.g. guanidine carbonate, as described above for the preparation of compounds of formula (1).

10 Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1) and it is to be understood that the invention extends to such interconversion processes. Thus, for example, standard substitution approaches employing for example Alkylation, arylation, heteroarylation, acylation, thioacylation, sulphonylation, formylation or coupling reactions may be used to add new substituents to
15 and/or extend existing substituents in compounds of formula (1). Alternatively existing substituents in compounds of formula (1) may be modified by for example oxidation, reduction or cleavage reactions to yield other compounds of formula (1).

20

The following describes in general terms a number of approaches which can be employed to modify existing phenyl and/or other aromatic or heteroaromatic groups in compounds of formula (1). It will be appreciated that each of these reactions will only be possible where an appropriate
25 functional group exists in a compound of formula (1). Where desired, these reactions may also be performed on intermediates to compounds of formula (1).

Thus, for example Alkylation, arylation or heteroarylation of a compound of
30 formula (1) may be achieved by reaction of the compound with a reagent Alk, L or ArL, where Alk is an Alkyl group and Ar is an aryl or heteroaryl

group as defined above in relation to compounds of formula (1) and L is a leaving atom or group such as a halogen atom, e.g. a chlorine or bromine atom, or a sulphonyloxy group, e.g. an arylsulphonyloxy group such as a *p*-toluenesulphonyloxy group.

5

- The Alkylation or arylation reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or potassium carbonate, an Alkoxide, e.g. potassium *t*-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at around 0°C to around 40°C.

10

- In a variation of this process the leaving group L may be alternatively part of the compound of formula (1) and the reaction performed with an appropriate nucleophilic reagent at an elevated temperature. Particular nucleophilic reagents include cyclic amines, such as piperazine. Where appropriate the reaction may be performed in a solvent such as an aprotic solvent, e.g. a substituted amide such as dimethylformamide.

15

- In another general example of an interconversion process, a compound of formula (1) may be acylated or thioacylated. The reaction may be performed for example with an acyl halide or anhydride in the presence of a base, such as a tertiary amine e.g. triethylamine in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at for example ambient temperature, or by reaction with a thioester in an inert solvent such as tetrahydrofuran at a low temperature such as around 0°C. The reaction is particularly suitable for use with compounds of formula (1) containing primary or secondary amino groups.

25

- In a further general example of an interconversion process, a compound of formula (1) may be formylated, for example by reaction of the compound with a mixed anhydride HCOOCOCH_3 or with a mixture of formic acid and acetic anhydride.

30

- Compounds of formula (1) may be prepared in another general interconversion reaction by sulphonylation, for example by reaction of the

35

compound with a reagent $\text{AlkS(O)}_2\text{L}$, or $\text{ArS(O)}_2\text{L}$ in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature. The reaction may in particular be performed with compounds of formula (1) possessing a primary or secondary amino group.

In further examples of interconversion reactions according to the invention compounds of formula (1) may be prepared from other compounds of formula (1) by modification of existing functional groups in the latter.

Thus in one example, ester groups $-\text{CO}_2\text{Alk}^1$ in compounds of formula (1) may be converted to the corresponding acid $[-\text{CO}_2\text{H}]$ by acid- or base-catalysed hydrolysis or by catalytic hydrogenation depending on the nature of the group Alk^1 . Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an Alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol. Catalytic hydrogenation may be carried out using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol, e.g. methanol.

In a second example, $-\text{OAlk}$ [where Alk represents an Alkyl group such as a methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol $-\text{OH}$ by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C .

In another example, alcohol $-\text{OH}$ groups in compounds of formula (1) may be converted to a corresponding $-\text{OAlk}$ or $-\text{OAr}$ group by coupling with a reagent AlkOH or ArOH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [-NHSO₂NH₂] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [-NH₂] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

5

In another example of an interconversion process secondary amine groups in compounds of formula (1) may be Alkylated using an alcohol, e.g. ethanol and catalytic hydrogenation, employing for example hydrogen in the presence of a metal catalyst such as palladium on a support such as carbon.

10

In a further example, amine [-NH₂] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature. In an alternative, amine groups may also be generated by reduction of the corresponding nitrile, for example using a reducing agent such as a borohydride, e.g. sodium borohydride or cerium trichloride.

15

In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation as just described, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

20

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

25

30

Where salts of compounds of formula (1) are desired, these may be prepared by conventional means, for example by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent or mixture of solvents, e.g. an organic solvent such as an ether, e.g. diethylether, or an alcohol, e.g. ethanol.

35

The following Examples illustrate the invention. In the Examples all ^1H nmr were run at 300MHz unless specified otherwise. All temperatures are in $^{\circ}\text{C}$.

5 The following abbreviations are used:

THF - tetrahydrofuran;

DMF - dimethylformamide;

DMSO - dimethylsulphoxide;

TFA - trifluoroacetic acid;

10 **EXAMPLE 1**

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine

A mixture of 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.53g, 4.0mmol) and 4-aminophenethyl alcohol (1.10g, 8.0mmol) in 2-ethoxyethanol (15ml) was heated to reflux for 18h. The reaction was cooled to room temperature, trifluoroacetic acid (2ml) added and the reaction stirred for 30min. Solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (100ml) and saturated, aqueous Na_2CO_3 (80ml). The aqueous layer was re-extracted with CH_2Cl_2 (2 x 80ml) and the combined CH_2Cl_2 layer washed with aqueous Na_2CO_3 (80ml), brine (80ml), dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 10-15% methanol in CH_2Cl_2) to give the title compound as a buff solid (1.30g) m.p. 162-163 $^{\circ}$. δH (d^6DMSO) 9.74 (1H, s), 8.55 (1H, s), 7.76 (2H, d, \downarrow 8.5Hz), 7.68 (2H, d, \downarrow 8.5Hz), 7.62 (2H, d, \downarrow 8.5Hz), 7.12 (2H, d, \downarrow 8.5Hz), 4.57 (1H, bs), 3.55 (2H, m), 2.65 (2H, t, \downarrow 7.2Hz), 1.41 (6H, s); MS (ESI) 383 (MH^+ , ^{35}Cl , 100%).

The 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine used in the above process was prepared as follows:-

30 Cerium trichloride heptahydrate (22.47g, 60mmol) was dried in a flask under high vacuum (0.08 Torr) heated by an oil bath at 140-160 $^{\circ}$ for 4h. On cooling, nitrogen was introduced slowly into the flask and anhydrous THF (120ml) added to give a suspension of CeCl_3 which was stirred for 16h at room temperature. The mixture was cooled to -65 $^{\circ}$, methyl lithium 35 (37.5ml of a 1.6M solution in diethylether, 60mmol) added dropwise and the mixture stirred for 0.5h. A solution of 4-bromobenzonitrile (3.64g,

- 20mmol) in THF (10ml) was added and the reaction stirred at -65° for 3.5h before allowing the mixture to warm to -40° . The reaction was quenched by the addition of 33% ammonium hydroxide (50ml) and then allowed to warm to room temperature. The resulting solids were removed by filtration through a pad of Celite® and were washed with ethyl acetate (3 x 100ml). The combined filtrates were washed with brine (20ml), the organic phase dried (MgSO_4) and concentrated *in vacuo* to give 1-(4-bromophenyl)-1-methylethylamine as a yellow oil (4.01g). This product was heated at reflux in toluene (40ml) with di-tert-butyl dicarbonate (4.50g, 20.6mmol) for 1h. Solvent was removed *in vacuo* and the crude product recrystallised from hexane at -20° to give tertbutyl N-{1-(4-bromophenyl)-1-methylethyl}carbamate as colourless crystals (3.47g) m.p. $92-93^{\circ}$ δH (CDCl_3) 7.43 (2H, dt, \downarrow 8.7, 2.7Hz), 7.26 (2H, dt, \downarrow 8.8, 2.6Hz), 4.91 (1H, bs), 1.59 (6H, s), 1.36 (9H, bs).
- 15 A mixture of tert-butyl N-{1-(4-bromophenyl)-1-methylethyl}carbamate (1.57g, 5.0mmol), bis(pinacolato)diboron (1.40g, 5.5mmol), [1,1'-bis (diphenylphosphino)ferrocene]dichloropalladium(II) (123mg, 0.015mmol) and potassium acetate (1.47g, 15.0mmol) was dissolved in dry DMF (20ml) under nitrogen and heated to 80° for 5h. The reaction was then concentrated under reduced pressure, the resulting residue taken up in dichloromethane (80ml) and washed with water (1 x 80ml), then brine (1 x 80ml), dried (MgSO_4) and again concentrated. The residue was subjected to column chromatography (silica gel; 15% ethyl acetate-hexane) to give tert-butyl N-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methylethyl}carbamate (1.55g) as a white solid m.p. 140° . δH (CDCl_3) 7.77 (2H, d, \downarrow 8.3Hz), 7.40 (2H, d, \downarrow 8.4Hz), 1.63 (6H, s) and 1.34 (21H, s).
- 20 2M aqueous Na_2CO_3 (4.7ml, 9.4mmol) was added to a solution of 2,4,5-trichloropyrimidine [Chesterfield, J.; McOmie, J. F. W.; Sayer, E. R.; J. Chem. Soc. (1955) 3478-3481] (1.18g, 6.44mmol), tert-butyl N-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methylethyl}carbamate (1.55g, 4.29mmol) and tetrakis(triphenylphosphine)palladium (O) (150mg, 0.13mmol) in ethyleneglycol dimethylether (20ml) under N_2 and the mixture heated to reflux for 6h. The reaction was diluted with H_2O (30ml) and extracted with ethyl acetate (3 x 50ml), the combined ethyl acetate extracts were washed with brine (30ml), dried (MgSO_4) and

concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, 15% ethyl acetate in hexane) to give 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine as a white solid (1.34g). δ H (d⁶DMSO) 8.62 (1H, s), 7.90 (2H, d, \downarrow 8.6Hz), 7.54 (2H, dt, \downarrow 8.7, 2.1Hz), 5.02 (1H, bs), 1.65 (6H, s) and 1.37 (9H, s).

EXAMPLE 2

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[3-(2-hydroxyethyl)phenyl]pyrimidine-2-amine

The title compound was prepared from 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.50g, 6.55mmol) and 2-(3-aminophenyl)ethanol (942mg, 6.87mmol) following the method of Example 1. The crude product was purified by chromatography (Silica, 10% methanol in CH₂Cl₂) to give the title compound as a brown solid (600mg) m.p. 184-185°. δ H (d⁶DMSO) 9.77 (1H, s), 8.57 (1H, s), 7.79 (2H, d, \downarrow 8.4Hz), 7.68 (2H, d, \downarrow 8.4Hz), 7.61-7.58 (2H, m), 7.17 (1H, t, \downarrow 7.7Hz), 6.82 (1H, d, \downarrow 7.4Hz), 4.62 (1H, bs), 3.60 (2H, t, \downarrow 7.0Hz), 2.68 (2H, t, \downarrow 7.1Hz), 2.07 (2H, bs), 1.41 (6H, s); MS (ESI) 383 (MH⁺, ³⁵Cl).

EXAMPLE 3

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(1-imidazolyl)phenyl]pyrimidine-2-amine

Sodium hydride (330mg, 8.25mmol) was added to a solution of 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.0g, 2.62mmol) and 1-(4-aminophenyl)-1H-imidazole (438mg, 2.75mmol) in dry THF (40ml) under N₂ and the mixture heated to reflux for 3h. The reaction was quenched with H₂O (5ml), diluted with brine (50ml) and extracted with ethyl acetate (2 x 150ml). The ethyl acetate extracts were dried (MgSO₄), concentrated *in vacuo* and the residue purified by column chromatography (silica; 2% ethyl acetate in CH₂Cl₂) to give 4-[4-(1-tert-butoxy carbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(1-imidazolyl)-phenyl] pyrimidine-2-amine as a yellow solid (310mg) m.p. 218-220°. This intermediate was stirred at room temperature in trifluoroacetic acid (4ml) for 3h before concentrating the reaction *in vacuo*. The residue was diluted with 2M NaOH (aq) (50ml) and extracted with CH₂Cl₂-ethanol (20:1) (3 x 50ml), the extracts dried (MgSO₄) and concentrated *in vacuo*. Trituration

of the resultant solid with diethylether-ethyl acetate (4:1) gave the title compound as a pale yellow solid (175mg) m.p. 199-201°. δ H (d^6 DMSO) 10.05 (1H, bs), 8.62 (1H, s), 8.15 (1H, s), 7.88 (2H, d, \downarrow 7.9Hz), 7.78 (2H, d, \downarrow 8.5Hz), 7.69 (2H, d, \downarrow 8.5Hz), 7.65 (1H, s), 7.55 (2H, d, \downarrow 8.8Hz), 1.42 (6H, s). MS (ESI) 405 (MH⁺, 100%).

1-(4-Aminophenyl)-1H-imidazole used in the above process was prepared by suspending 1-(4-nitrophenyl)-1H-imidazole (10.0g, 52.86mmol) and 10% Pd on carbon (1g) in ethanol (125ml). The mixture was degassed with N₂ and subjected to an atmosphere of hydrogen (balloon) for 24h at room temperature with magnetic stirring. The reaction was filtered through Celite®, washing the filter cake with ethanol (125ml) and the filtrates concentrated *in vacuo* to give 1-(4-aminophenyl)-1H-imidazole as an off white solid (8.02g) m.p. 156-157°.

15 EXAMPLE 4

4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine

The title compound was prepared from 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine (1.60g, 4.0mmol) and 4-aminophenethyl alcohol (826mg, 6.0mmol) following the method of Example 1.

The crude product was purified by column chromatography (silica; 5-10% MeOH in CH₂Cl₂) to give the title compound as a light brown solid (920mg) m.p. 172-176°. δ H (CDCl₃) 8.43 (1H, s), 7.67 (1H, dd, \downarrow 8.2, 1.8Hz), 7.62-7.55 (4H, m), 7.22 (2H, d, \downarrow 8.5Hz), 7.19 (1H, bs), 3.86 (2H, t, \downarrow 6.5Hz), 2.86 (2H, t, \downarrow 6.5Hz), 1.68 (2H, bs), 1.60 (6H, s). MS (ESI) 401 (MH⁺).

The intermediate 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine in the above process was prepared using the same methods described for its analogue in Example 1. Thus starting from 4-bromo-2-fluorobenzonitrile the following intermediates were prepared:

tert-Butyl *N*-{1-(4-bromo-2-fluorophenyl)-1-methylethyl}carbamate as an off white solid δ H (CDCl₃) 7.25-7.16 (3H, m), 4.98 (1H, bs), 1.66 (6H, s), 1.36 (9H, bs).

tert-Butyl *N*-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxanborolan-2-yl)-2-

fluorophenyl]-1-methylethyl)carbamate as a white solid δ H (CDCl₃) 7.51 (1H, dd, \downarrow 7.7, 1.1Hz), 7.42 (1H, dd, \downarrow 13.0, 1.1Hz), 7.34 (1H, t, \downarrow 8.0Hz), 5.01 (1H, bs), 1.68 (6H, s), 1.33 (21H, bs).

- 5 4-[4-(1-tertButoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine m.p. 148-149°. δ H (CDCl₃) 8.65 (1H, s), 7.72 (1H, dd, \downarrow 8.3, 1.9Hz), 7.64 (1H, dd, \downarrow 13.1, 1.8Hz), 7.50 (1H, t, \downarrow 8.3Hz), 5.04 (1H, bs), 1.72 (6H, s), 1.37 (9H, s) MS (ESI) 422 (MNa⁺).

EXAMPLE 5

- 10 4-[4-(1-Allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

- p-Toluenesulphonyl chloride (867mg, 4.55mmol) was added to a solution of 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (1.16g, 3.03mmol), pyridine
15 (2.45ml, 30.3mmol) and 4-dimethylaminopyridine (50mg) in CH₂Cl₂ (25ml). The reaction was stirred at room temperature under N₂ for 18h before diluting with CH₂Cl₂ (50ml). The dichloromethane solution was washed with 2M hydrochloric acid (2 x 80ml), brine (80ml), dried (MgSO₄) and concentrated *in vacuo* to give a thick oil. Column chromatography
20 (silica; 35% ethyl acetate in hexane) gave 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-ptoluenesulphonyloxyethyl)phenyl]pyrimidine-2-amine as a pale yellow solid (1.40g). δ H (CDCl₃) 8.42 (1H, s), 7.89 (2H, d, \downarrow 8.5Hz), 7.70 (2H, dt, \downarrow 8.4, 1.8Hz), 7.56-7.51 (5H, m), 7.28 (2H, d, \downarrow 8.6Hz), 7.09 (2H, d, \downarrow 8.5Hz), 5.90 (1H, bs), 5.32 (1H, bs),
25 5.21 (2H, s), 4.51 (2H, d, \downarrow 5.5Hz), 4.20 (2H, t, \downarrow 7.1Hz), 2.93 (2H, t, \downarrow 7.1Hz), 2.41 (3H, s), 1.71 (6H, s).

- To the tosylate prepared above (1.0g, 1.61mmol) in dry DMF (20ml) under N₂ was added imidazole (1.03g, 15.2mmol) and the mixture heated to 80° for 18h. Solvent was removed *in vacuo* and the residue dissolved in
30 CH₂Cl₂ (80ml), washed with aqueous Na₂CO₃ (3 x 20ml), brine (20ml), dried (MgSO₄) and concentrated *in vacuo*. Column chromatography (silica; 5% methanol in CH₂Cl₂) gave 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-imidazol-1-ylethyl)phenyl]pyrimidine-2-amine as a yellow solid (670mg) m.p. 72-78°. δ H (CDCl₃) 8.41 (1H, s)
35 7.88 (2H, d, \downarrow 8.6Hz), 7.61-7.52 (4H, m), 7.35 (1H, bs), 7.21 (2H, d, \downarrow

8.5Hz), 5.89 (1H, bs), 5.39-5.13 (3H, m), 4.50 (2H, d, \downarrow 5.6Hz), 3.86 (2H, t, \downarrow 6.5Hz), 2.85 (2H, t, \downarrow 6.5Hz), 1.71 (6H, s). MS (ESI) 517 (MH⁺, 100%).

The intermediate 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-hydroxy-ethyl)phenyl]pyrimidine-2-amine used in the above

5 process was prepared as follows:

To a solution of the compound of Example 1 (1.20g, 3.1mmol) in CH₂Cl₂ (40ml) was added saturated, aqueous Na₂CO₃ (20ml) and allylchloroformate (410mg, 3.4mmol) and the reaction stirred at room temperature for 2h. The CH₂Cl₂ layer was separated, dried (MgSO₄) and

10 concentrated *in vacuo*. The crude material was purified by column chromatography (silica; 5% methanol in CH₂Cl₂) to give the desired intermediate as a yellow solid (1.23g). δ H (CDCl₃) 8.41 (1H, s), 7.88 (2H, d, \downarrow 8.6Hz), 7.61-7.51 (4H, m), 7.35 (1H, bs), 7.21 (2H, d, \downarrow 8.5Hz), 6.91 (1H, bs) 5.40-5.18 (3H, m), 4.50 (2H, d, \downarrow 5.6Hz), 3.86 (2H, t, \downarrow 6.5Hz),

15 2.85 (2H, t, \downarrow 6.5Hz), 1.71 (6H, s). MS (ESI) 467 (MH⁺, 100%).

EXAMPLE 6

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-morpholinoethyl)phenyl]pyrimidine-2-amine

20 A mixture of the tosylate prepared in Example 5 (400mg, 0.64mmol) and morpholine (0.28ml, 3.22mmol) was heated to reflux in dry THF (10ml) under N₂ for 18h. The reaction was diluted with ethyl acetate (40ml), washed with saturated, aqueous Na₂CO₃ (2 x 20ml), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column

25 chromatography (4% methanol in CH₂Cl₂) to give the title compound as a yellow solid (310mg) m.p. 65-69° δ H (CDCl₃) 8.41 (1H, s) 7.88 (2H, d, \downarrow 8.5Hz), 7.57-7.52 (4H, m), 7.19 (2H, d, \downarrow 8.4Hz), 7.18 (1H, obscured by over-lapping signal), 5.88 (1H, bs), 5.36-5.19 (3H, m), 4.50 (2H, d, \downarrow 5.6Hz), 3.85 (4H, bs), 3.06-2.43 (8H, m), 1.71 (6H, s).

30

EXAMPLE 7

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

The title compound was prepared from 4-[4-(1-allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-*p*-toluenesulphonyloxyethyl)-phenyl]pyrimidine-2-amine (504mg, 0.79mmol) and imidazole (337mg,

35

4.95 mmol) following the method described for Example 5. The crude product was purified by column chromatography (silica; 5% methanol in CH₂Cl₂) to give the title compound as a yellow solid (330mg) m.p. 88° forms gum. δ H (CDCl₃) 8.43 (1H, s), 7.69 (1H, dd, \downarrow 8.2, 1.8Hz), 7.61 (1H, dd, \downarrow 13.3, 1.8Hz), 7.54 (2H, d, with fine splitting, \downarrow 8.6Hz), 7.50 (1H, t, \downarrow 8.5Hz), 7.34 (1H, s), 7.18 (1H, s), 7.04 (3H, m), 5.89 (1H, bs), 5.30-5.12 (3H, m), 4.50 (2H, dt, \downarrow 5.6, 1.4Hz), 4.16 (2H, t, \downarrow 7.1Hz), 3.03 (2H, t, \downarrow 7.0Hz), 1.78 (6H, s); MS (ESI) 535 (MH⁺, 100%).

The intermediate tosylate used in the above process was prepared using the same methods described for its analogue in Example 5: thus starting from the compound of Example 4 the following intermediates were prepared:

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine as a yellow solid. δ H (CDCl₃) 8.42 (1H, s), 7.69 (1H, d, \downarrow 8.2Hz), 7.61 (1H, d, \downarrow 13.4Hz), 7.56 (2H, d, \downarrow 8.4Hz), 7.49 (1H, t, \downarrow 8.4Hz), 7.22 (2H, d, \downarrow 8.5Hz), 7.21 (1H, bs), 5.88 (1H, bs), 5.30 (1H, s), 5.29-5.16 (2H, m), 4.49 (2H, m), 3.86 (2H, t, \downarrow 6.3Hz), 2.86 (2H, t, \downarrow 6.3Hz), 1.78 (6H, s); MS (ESI) 485 (MH⁺, 100%).

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-ptoluenesulphonyloxyethyl)phenyl]pyrimidine-2-amine as a yellow solid. δ H (CDCl₃) 8.43 (1H, s), 7.70 (4H, m), 7.62 (1H, dd, \downarrow 13.3, 1.8Hz), 7.54-7.48 (3H, m), 7.29 (2H, d, \downarrow 8.0Hz), 7.10 (2H, d, \downarrow 8.5Hz), 5.88 (1H, bs), 5.33-5.12 (3H, m), 4.51 (2H, m), 4.20 (2H, t, \downarrow 7.1Hz), 2.94 (2H, t, \downarrow 7.0Hz), 2.42 (3H, s), 1.78 (6H, s).

EXAMPLE 8

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

Tetrakis(triphenylphosphine)palladium(0) (147mg, 0.13mmol) was added to a solution of the compound of Example 5 (655mg, 1.27mmol) and 5,5-dimethyl-1,3-cyclohexanedione (1.42g, 10.15mmol) in anhydrous THF (20ml) under N₂. The reaction was stirred for 30min at room temperature and was then diluted with ethyl acetate (50ml), washed with 2M aqueous NaOH (3 x 20ml), brine (20ml), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography (Silica; 10% methanol in CH₂Cl₂) to give the title compound as a yellow solid (380mg).

δ H (CDCl₃) m 8.41 (1H, s), 7.86 (2H, d, \downarrow 8.5Hz), 7.64 (2H, d, \downarrow 8.5Hz), 7.55 (2H, d, \downarrow 8.5Hz), 7.36 (1H, bs), 7.34 (1H, bs), 6.99 (3H, m), 6.83 (1H, bs), 4.14 (2H, m), 3.00 (2H, t, \downarrow 7.0Hz), 2.72 (2H, bs), 1.57 (6H, s). MS (ESI) 433 (MH⁺, 100%).

5

The following examples 9 and 10 were prepared by the method described for Example 8.

EXAMPLE 9

10 **4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-morpholinoethyl)phenyl]pyrimidine-2-amine**

From the compound of Example 6 (310mg, 0.58mmol), tetrakis-(triphenylphosphine)palladium(O) (60mg, 0.06mmol) and 5,5-dimethyl-1,3-cyclohexadione (650mg, 4.64mmol) to give the title compound as a pale yellow solid (240mg) m.p. 166-173° δ H (CDCl₃) 8.40 (1H, s), 7.87 (2H, d, \downarrow 8.4Hz), 7.65 (2H, d, \downarrow 8.3Hz), 7.53 (2H, d, \downarrow 8.3Hz), 7.24 (1H, bs), 7.17 (2H, d, \downarrow 8.4Hz), 3.75 (4H, m), 2.78 (2H, m), 2.58 (8H, m), 1.58 (6H, s). MS (ESI) 452 (MH⁺).

20 **EXAMPLE 10**

4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-imidazol-1-yl)ethyl]phenyl]pyrimidine 2-amine

From the compound of Example 7 (330mg, 0.62mmol) tetrakis-(triphenylphosphine)palladium(O) (71mg, 0.062mmol) and 5,5-dimethyl-1,3-cyclohexadione (692mg, 4.94mmol) to give after chromatography (Silica; 8% methanol in CH₂Cl₂) the title compound as a yellow solid (200mg) m.p. 112-120° δ H (d⁶ DMSO) 9.85 (1H, s), 8.60 (1H, s), 7.77 (1H, t, \downarrow 8.4Hz), 7.62 (2H, d, \downarrow 8.5Hz), 7.57 (1H, s, with fine splitting), 7.52 (1H, d, \downarrow 1.7Hz), 7.48 (1H, s), 7.12 (1H, s), 7.08 (2H, d, \downarrow 8.5Hz), 6.83 (1H, s), 4.16 (2H, t, \downarrow 7.4Hz), 2.95 (2H, t, \downarrow 7.5Hz), 1.46 (6H, s), MS (ESI) 451 (MH⁺).

EXAMPLE 11

35 **Resin bound 4-[4-(1-tertbutoxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (1)**

A slurry of polystyrene sulphonyl chloride resin (Argonaut Technologies, 520mg, 2.4mmol/g, 1.24mmol equivalent) in anhydrous dichloromethane (12ml) was treated with 4-[4-(1-tertbutoxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (2.40g, 4.97mmol), N,N-diethylisopropylamine (0.64g, 4.97mmol) and anhydrous pyridine (4mL) and the resulting mixture agitated at room temperature for 18h. The resin was filtered and washed sequentially with dichloromethane, methanol, N,N-dimethylformamide and dichloromethane then air dried to give the sulphonate derivatised resin (1).

10

EXAMPLE 12

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

A mixture of derivatised resin (1) (55mg), N,N-diethylisopropylamine (38mg, 0.30mmol), and 2-methylimidazole (8mg, 0.10mmol) in anhydrous acetonitrile (2ml) was heated at 70° for 18h, with agitation. The mixture was allowed to cool to room temperature then diluted with anhydrous tetrahydrofuran (2ml) and treated with polystyrene methylisocyanate (Argonaut Technologies, 120mg, 1.65mmol/g, 0.2mmol equivalent) and macroporous triethylammonium methylpolystyrene carbonate (Argonaut Technologies, 38mg, 2.64mmol/g, 0.1mmol equivalent). The resulting mixture was agitated at room temperature for 6h, then filtered and washed once with dichloromethane. The combined filtrate and washings were evaporated to dryness under a stream of nitrogen, then resuspended in dichloromethane (1mL) and treated with trifluoroacetic acid (1mL) for 1h at room temperature. The mixture was evaporated to give the title compound (19.4mg).

25

HPLC-MS Retention time 1.93min; MH+ 447

HPLC-MS

HPLC-MS was performed on a Hewlett Packard 1100/MSD ES Single Quadropole system with diode array detector using a Luna C18(2) 50 x 2.0mm (3µm) column, running a gradient of 95% [0.1% aqueous formic acid], 5% [0.1% formic acid in acetonitrile] to 10% [0.1% aqueous formic acid], 90% [0.1% formic acid in acetonitrile] over 2min, then maintaining the mobile phase at that ratio for a further 1min. Flow rate 0.8ml/min. MS

35

was acquired by API electrospray in positive ion mode, at 70V, scanning from 150 to 750amu.

- 5 The following compounds of examples 13 to 25 were prepared in a similar manner to the compound of example 12, each using the starting material shown in place of 2-methylimidazole:

EXAMPLE 13

- 10 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-ethylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

2-Ethylimidazole gave the title compound (16.1mg)

HPLC-MS Retention time 1.96min; MH+ 461

EXAMPLE 14

- 15 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

2-Isopropylimidazole gave the title compound (12.8mg)

HPLC-MS Retention time 1.98min; MH+ 475

20 **EXAMPLE 15**

- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4,5-dichloroimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

4,5-Dichloroimidazole gave the title compound (20.4mg)

HPLC-MS Retention time 2.27min; MH+ 501

25

EXAMPLE 16

- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(benzimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine

Benzimidazole gave the title compound (16.4mg)

- 30 HPLC-MS Retention time 2.04min; MH+ 483

EXAMPLE 17

- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(thiomorpholino)ethyl)phenyl]pyrimidine-2-amine

- 35 Thiomorpholine gave the title compound (22.0mg)

HPLC-MS Retention time 1.93min; MH+ 468

EXAMPLE 18

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(tertbutylamino)ethyl)phenyl]pyrimidine-2-amine

- 5 tertButylamine gave the title compound (20.4mg)
HPLC-MS Retention time 1.94min; MH+ 438

EXAMPLE 19

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine

- 10 1-Methylpiperazine gave the title compound (17.4mg)
HPLC-MS Retention time 1.84min; MH+ 465

EXAMPLE 20

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine

- 15 1-Ethylpiperazine gave the title compound (22.1mg)
HPLC-MS Retention time 1.85min; MH+ 479

EXAMPLE 21

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3,5-dimethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine

- 20 2,6-Dimethylpiperazine gave the title compound (3.1mg)
HPLC-MS Retention time 1.93min; MH+ 479

EXAMPLE 22

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-(pyrid-2-yl)piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine

- 25 4-(Pyrid-2-yl)piperazine gave the title compound (15.3mg)
30 HPLC-MS Retention time 1.92min; MH+ 528

EXAMPLE 23

4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(pyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine

- 35 Pyrrolidine gave the title compound (5.6mg)
HPLC-MS Retention time 1.93min; MH+ 436

EXAMPLE 24**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(piperidin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

- 5 Piperidine gave the title compound (19.1mg)
HPLC-MS Retention time 1.94min; MH+ 450

EXAMPLE 25**(R)-4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3-dimethylaminopyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

- 10 (R)-3-Dimethylaminopyrrolidine gave the title compound (23.1mg)
HPLC-MS Retention time 1.75min; MH+ 479

EXAMPLE 26**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-morpholinoethyl)phenyl]pyrimidine-2-amine maleic acid salt**

- 15 To a hot solution of the compound of Example 9 (50mg, 0.11mmol) in ethanol (2ml) was added a solution of maleic acid (13mg, 0.11mol) in ethanol (1ml) and the mixture stirred at room temperature for 1h. The
20 solution was partially concentrated *in vacuo* and diethyl ether added to give the desired product as a white precipitate. The precipitate was collected by filtration and washed with diethyl ether to give the title compound as a white solid (49mg). m.p. 179-182°. δ H (d⁶ DMSO) 9.85 (1H, s), 8.64 (1H, s), 8.32 (1H, bs), 7.94 (2H, d, \downarrow 8.5Hz), 7.71 (2H, d, \downarrow 8.5Hz), 7.64 (2H, d, \downarrow 8.5Hz), 7.15 (2H, d, \downarrow 8.5Hz), 6.02 (2H, s), 3.61 (4H, bs), 3.31 (3H, bs), 2.69-2.50 (8H, m), 1.69 (6H, s).
- 25

BIOLOGICAL ACTIVITY

- 30 The following assays were used to demonstrate the activity and selectivity of compounds according to the invention:

The activity of the compounds against KDR kinase and FGFR2 kinase can be determined in the following two assays:

KDR Kinase and FGFr2 Kinase

The activities of recombinant KDR kinase and FGFr2 kinase were determined by measuring their ability to transfer the γ -phosphate from [^{33}P]ATP to polyglutamic acid - tyrosine (pEY).

5

The assay methodology employed for both kinases is identical except that in the assay of KDR kinase the diluent used throughout was 20mM HEPES pH 7.25 containing 2mM MnCl_2 , 2mM MnCl_2 , 5mM DTT and 0.05% Brij 35, whereas in the FGFr2 assay 10mM MnCl_2 is used instead of 2mM MnCl_2 and 2mM MnCl_2 .

10

The assay was conducted in a total volume of 202 μl containing 1-10ng kinase, 5 $\mu\text{g/ml}$ pEY (4:1) (Sigma, UK), 1 μM ATP (containing ~50,000cpm [^{33}P]ATP (Amersham International, UK) (Sigma, UK) and test inhibitors at the appropriate concentration. The test inhibitors were dissolved in DMSO and added such that the final concentration of DMSO in the assay did not exceed 2% (v/v). The assay was initiated by addition of kinase and terminated after 10 minutes incubation at room temperature by addition of 50 μl of 20mM HEPES pH 7.25 containing 0.125M EDTA and 10mM ATP. A 200 μl aliquot was applied to the well of a Millipore (UK) MAFC filter plate containing 100 μl of 30% (w/v) trichloroacetic acid (TCA). The plate was then placed on a suitable manifold and connected to a vacuum. After complete elimination of the liquid each well was washed under vacuum using five volumes (100 μl per wash) of 10% (w/v) TCA and finally two volumes (100 μl per wash) of ethanol. The bottom of the filter plate was then sealed and 100 μl per well of Ultima Gold (Beckham, UK) scintillant was added to each well. The radioactivity was measured using an appropriate scintillation counter such as a Wallac Trilux or Packard TopCount. The IC_{50} value for each inhibitor was obtained from log dose inhibition curves fitted to the four-parameters logistic equation.

15

20

25

30

In this assay the most active compounds according to the invention have IC_{50} values of around 1 μM and below.

35 The selectivity of compounds according to the invention can be determined in the following assays:

p56^{lck} kinase assay

The tyrosine kinase activity of p56^{lck} was determined using a RR-src peptide (RRLIEDNEYTARG) and [γ -³³P]ATP as substrates. Quantitation of the ³³P-phosphorylated peptide formed by the action of p56^{lck} was achieved using an adaption of the method of Geissler *et al* (J. Biol. Chem. (1990) 265, 22255-22261).

All assays were performed in 20mM HEPES pH 7.5 containing 10mM MgCl₂, 10mM MnCl₂, 0.05% Brij, 1 μ M ATP (0.5 μ Ci[γ -³³P]ATP) and 0.8mg/ml RR-src. Inhibitors in dimethylsulphoxide (DMSO) were added such that the final concentration of DMSO did not exceed 1%, and enzyme such that the consumption of ATP was less than 10%. After incubation at 30°C for 15min, the reaction was terminated by the addition of one-third volume of stop reagent (0.25mM EDTA and 33mM ATP in dH₂O). A 15 μ l aliquot was removed, spotted onto a P-30 filtermat (Wallac, Milton Keynes, UK), and washed sequentially with 1% acetic acid and de-ionised water to remove ATP. The bound ³³P-RR-src was quantitated by scintillation counting of the filtermat in a Betaplate scintillation counter (Wallac, Milton Keynes, UK) after addition of Meltilex scintillant (Wallac, Milton Keynes, UK).

The dpm obtained, being directly proportional to the amount of ³³P-RR-src produced by p56^{lck}, were used to determine the IC₅₀ for each compound. The IC₅₀ was defined as the concentration of compound required to reduce the production of ³³P-RR-src by 50%.

In this test, compounds according to the invention have IC₅₀ values of 10 μ M and above.

30

Zap-70 kinase assay

The tyrosine kinase activity of Zap-70 was determined using a capture assay based on that employed above for p56^{lck}. The RR-src peptide was replaced with polyGlu-Tyr (Sigma; Poole, UK) at a final concentration of 17 μ g/ml. After addition of the stopped reaction to the filtermat, trichloroacetic acid 10% (w/v) was employed as the wash reagent instead of acetic acid

35

and a final wash in absolute ethanol was also performed before scintillation counting. IC₅₀ values were determined as described above in the p56^{lck} assay.

- 5 In this test the compounds of the invention have IC₅₀ values of around 10µM and above.

EGFr kinase assay

- 10 The tyrosine kinase activity of the EGF receptor (EGFr) was determined using a similar methodology to the p56^{lck} kinase assay, except that the RR-src peptide was replaced by a peptide substrate for EGFr obtained from Amersham International plc (Little Chalfont, UK) and used at the manufacturer's recommended concentration. IC₅₀ values were determined as described previously in the p56^{lck} assay.

15

Protein kinase C assay

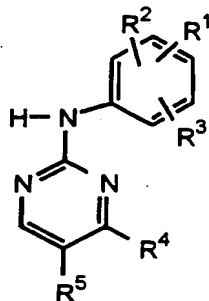
- 20 Inhibitor activity against protein kinase C (PKC) was determined using PKC obtained from Sigma Chemical Company (Poole, UK) and a commercially available assay system (Amersham International plc, Amersham, UK). Briefly, PKC catalyses the transfer of the γ-phosphate (³²p) of ATP to the threonine group on a peptide specific for PKC. Phosphorylated peptide is bound to phosphocellulose paper and subsequently quantified by scintillation counting. The inhibitor potency is expressed as either (i) the concentration required to inhibit 50% of the enzyme activity (IC₅₀) or (ii) the percentage inhibition achieved by 10µM inhibitor.
- 25

In this test the compounds of the invention have IC₅₀ values of around 10µM and above.

30

CLAIMS

1. A compound of formula (1):



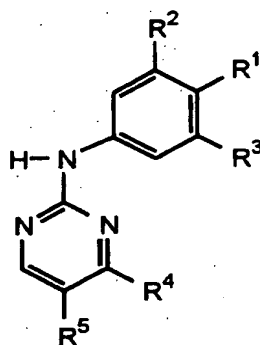
(1)

- 5
- 10 wherein R¹ is a -XR⁶ group [where X is a covalent bond, -O-, -S-, -C(O)-, -C(S)-, -C(O)O-, -S(O)-, -S(O)₂-, -CH₂-, or N(R⁷)- [where R⁷ is a hydrogen atom or a straight or branched alkyl group] and R⁶ is a hydrogen or halogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, or a -NO₂, -CN, -SO₂N(R⁸)(R⁹) [where R⁸ and R⁹, which may be the same or different is a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], -CON(R⁸)(R⁹), -CSN(R⁸)(R⁹), -NH₂ or substituted amino group;
- 15 R² and R³ which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, -OR¹⁰ [where R¹⁰ is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, -NO₂, -CN, -SR¹⁰, -COR¹⁰, S(O)R¹⁰, -SO₂R⁸, -SO₂N(R⁸)(R⁹), -CO₂R⁸, -CON(R⁸)(R⁹), -CSN(R⁸)(R⁹), -NH₂ or substituted amino group;
- 20 R⁴ is a X¹R¹¹ group where X¹ is a covalent bond or a -C(R¹²)(R¹³)- [where each of R¹² and R¹³ is a hydrogen or halogen atom or a hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R¹¹ is an optionally substituted phenyl, thienyl, thiazolyl or indolyl group;
- 25 R⁵ is a halogen atom or an alkynyl group;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein R⁵ is a bromine or chlorine atom.
- 5 3. A compound according to Claim 1 or Claim 2 wherein R⁴ is a X¹R¹¹ group in which X¹ is a covalent bond.
- 10 4. A compound according to any one of Claim 1 to Claim 3 wherein R⁴ is a X¹R¹¹ group and R¹¹ is a phenyl or substituted phenyl group containing one, two, or three R¹⁷ substituents in which each R¹⁷ substituent is an atom or group R¹⁸ or -Alk(R¹⁸)_m, where R¹⁸ is a halogen atom, or an amino (-NH₂), -NHR¹⁹ [where R¹⁹ is an -Alk(R¹⁸)_m, heterocycloaliphatic, -Alk-heterocycloaliphatic, aryl or heteroaryl group], -N(R¹⁹)₂ [where each R¹⁹ group is the same or different], nitro, cyano, hydroxyl (-OH), -OR¹⁹, formyl, carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), -SR¹⁹, -COR¹⁹, -CSR¹⁹, -SO₃H, -SO₂R¹⁹, -SO₂NH₂, -SO₂NHR¹⁹, SO₂N[R¹⁹]₂, -CONH₂, -CSNH₂, -CONHR¹⁹, -CSNHR¹⁹, -CON[R¹⁹]₂, -CSN[R¹⁹]₂, -N(R¹⁴)SO₂H [where R¹⁴ is a hydrogen atom or a C₁₋₆alkyl group], -N(R¹⁴)SO₂R¹⁹, -N[SO₂R¹⁹]₂, -N(R¹⁴)SO₂NH₂, -N(R¹⁴)SO₂NHR¹⁹, -N(R¹⁴)SO₂N[R¹⁹]₂, -N(R¹⁴)COR¹⁹, -N(R¹⁴)CONH₂, -N(R¹⁴)CONHR¹⁹, -N(R¹⁴)CON[R¹⁹]₂, -N(R¹⁴)CSR¹⁹, -N(R¹⁴)CSNH₂, -N(R¹⁴)CSNHR¹⁹, -N(R¹⁴)CSN[R¹⁹]₂, -N(R¹⁴)C(O)OR¹⁹, or an optionally substituted cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk is a straight or branched C₁₋₆ alkylene, C₂₋₆ alkenylene or C₂₋₆ alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or S(O)-, -S(O)₂- or -N(R¹⁴)- groups; and m is zero or an integer 1, 2 or 3.
- 15 5. A compound according to any one of Claim 1 to Claim 4 wherein one or both of R² and R³ is a hydrogen atom.
- 20 6. A compound according to Claim 5 wherein R² and R³ is each a hydrogen atom.
- 25 30 35

7. A compound according to any one of Claim 1 to Claim 6 wherein R¹ is a group $-(\text{Alk}^2)_p\text{NH}_2$ (where Alk² is a straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene chain, optionally substituted by one, two or three -O- or -S- atoms or -S(O)-, -S(O)₂- or -N(R¹⁴)- group [where R¹⁴ is a hydrogen atom or a C₁₋₆alkyl group] and p is zero or an integer 1), $-(\text{Alk}^2)_p\text{NR}^{15}\text{R}^{16}$ [where R¹⁵ is an optionally substituted C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl group optionally interrupted by an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R¹⁴)-, -CON(R¹⁴)-, -OC(O)N(R¹⁴)-, -CSN(R¹⁴)-, -N(R¹⁴)CO-, -N(R¹⁴)C(O)O-, -N(R¹⁴)CS-, -SON(R¹⁴), -SO₂N(R¹⁴), -N(R¹⁴)SO₂-, -N(R¹⁴)CON(R¹⁴)-, -N(R¹⁴)CSN(R¹⁴)-, -N(R¹⁴)SON(R¹⁴)- or -N(R¹⁴)SO₂N(R¹⁴) group and R¹⁶ is a hydrogen atom or a group as just defined for R¹⁵], $-(\text{Alk}^2)_p\text{NHet}^2$ (where -NHet² is an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group), $-(\text{Alk}^2)_p\text{OH}$ or $-(\text{Alk}^2)_p\text{Ar}$ (where Ar is a nitrogen-containing heteroaromatic group).
8. A compound according to Claim 7 wherein R¹ is a group $-\text{Alk}^2\text{NH}_2$, $-\text{Alk}^2\text{NR}^{15}\text{R}^{16}$, $-(\text{Alk}^2)_p\text{NHet}^2$ (where -NHet² is an optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl group), $-\text{Alk}_2\text{OH}$ or $-\text{Alk}^2\text{Ar}$ (where Ar is an optionally substituted imidazolyl or benzimidazolyl group).
9. A compound of formula (1a):



(1a)

wherein R¹, R², R³, R⁴ and R⁵ is each as defined in any one of Claim 1 to Claim 8.

- 5 10. A compound which is:
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-hydroxyethyl)
phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[3-(2-hydroxyethyl)
phenyl]pyrimidine-2-amine;
10 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(1-imidazolyl)
phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-
hydroxyethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(imidazol-1-
15 yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(2-
methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(2-
isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
20 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-
thiomorpholino)ethyl]phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(tertbutylamino)
ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(4-
25 methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(4-
ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(3,5-dimethyl-
piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
30 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(4-(pyrid-2-yl)
piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(pyrrolidin-1-
yl)ethyl)phenyl]pyrimidine-2-amine;
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-(piperidin-1-
35 yl)ethyl)phenyl]pyrimidine-2-amine;

and the salts, solvates, hydrates and N-oxides thereof.

11. A pharmaceutical composition comprising a compound according to
any one of the preceding claims together with one or more
5 pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04043

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/42 C07D401/12 A61K31/505 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 958 935 A (PETER-DAVID DAVIS) 28 September 1999 (1999-09-28) column 1 -column 10; claims	1-3, 11
A	WO 99 01439 A (DU PONT) 14 January 1999 (1999-01-14) claims	1-3, 11

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

14 March 2001

Date of mailing of the international search report

23/03/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/04043

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5958935 A	28-09-1999	AU 7631496 A EP 0862560 A WO 9719065 A	11-06-1997 09-09-1998 29-05-1997
WO 9901439 A	14-01-1999	AU 8181098 A EP 0994860 A US 6103737 A	25-01-1999 26-04-2000 15-08-2000

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.